REMARKS

Claims 26-57 are pending. Claims 26-39, 47, and 49-57 are withdrawn. Claims 40-46, and 48 are rejected. Claim 40 is amended to clarify the nucleic acid, with support found at least in originally filed claims 26 and 40, and to clarify the control, with support found at least at p. 10 lines 15-18. Claim 58 is added with support found at least at Examples 1, 2, and 5. Thus, Applicants assert that no new matter has been added.

CLAIM REJECTIONS UNDER 35 U.S.C. §112

Claims 40-46 and 48 are rejected under 35 U.S.C. 112 ¶1 as not enabled. Applicants respectfully disagree.

The Examiner states

> the specification does not provide any guidance on if an increase or decrease level of nucleic acid is predictive of graft reaction in a patient. For example, the specification does not indicate or provide any guidance that an increase or decrease, and how much increase and decrease of SEQ ID NO. 7 would be predictive of a rejection or tolerance of a graft in a human or any other organism.

The specification describes that the expression of T8 (SEQ ID NO. 7) is highly expressed in grafts of tolerance developing receptor animals (p. 21 lines 15-18), that T8 is strongly expressed in permanently accepted grafts, and that T8 is drastically decreased at the time of rejection (p. 18 lines 27-29). Thus, the specification describes that a stably high expression in SEQ ID NO. 7 is predictive of tolerance, and a reduced SEQ ID NO. 7 expression is predictive of graft rejection. The specification describes "how much increase or decrease of SEQ ID NO. 7" as a detectable changes in the level as compared to the control level (p. 10 lines 19-23). Applicants respectfully assert that a person having ordinary skill in the art would recognize that detectable changes in the level of SEQ ID NO. 7 are those changes that can be distinguished from the control level, e.g., based on statistical analysis. Thus, the specification enables a person having ordinary skill in the art to practice the method by determining that a detectable increase in the level of SEQ ID NO. 7, compared to a control level, indicates graft tolerance, and that a detectable decrease in the level of SEQ ID NO. 7, compared to a control level, indicates graft rejection.

The Examiner also states

> the specification teaches that rejection reaction, course of rejection, and rejection crisis is detected by an increased level of nucleic acid (see pg. 12 lines 16-30) and teaches that tolerance and course of tolerance is detected by an increased level of nucleic acid (see pg. 13 lines 13-28). Thus, based on the guidance in the specification it is unpredictable to determine an increased level of SEQ ID NO. 7 to determine graft reaction, as both a tolerance and rejection would be indicated by increased levels of SEQ ID NO. 7.

This in accurate. Page 12 describes SEQ ID NOs. 1 and 2, while p. 13 describes SEQ ID NOs. 3-8. Thus, when the rejection reaction is determined using SEQ ID NO. 7, an increase in the level of the nucleic acid indicates tolerance. Therefore, the determination of rejection reaction is predictable because an increased level of SEQ ID NO. 7 only indicates tolerance.

The Examiner states

> the specification does not indicate nor provide guidance that this sequence is also present in other organisms, and even if this sequence was present in other organisms, the specification provides no guidance on how the level of this sequence would be indicative of graft reaction in other species.

Example 5 describes that human homologs of the sequences have been identified. In addition,

Applicants submit with this Amendment a nucleotide base alignment between the rat and human sequence of SEQ ID NO. 7 (Exhibit A) which not only demonstrates existence of a human homolog of SEQ ID NO. 7, but also that the human homolog exhibits over 81% identity with the rat sequence. In addition, it is routine for a person having ordinary skill in the art to identify homologous mRNA in related species. Further, Example 5 shows that several of the described sequences exhibit regulation in human patients which is very similar to that observed in the animal models. Therefore, "how the level of this sequence would be indicative of graft reaction in other species" would be determined as described above, namely, comparing the level of the nucleic acid with a control, and determining if there were detectable changes. Thus, Applicants respectfully assert that the specification does enable a person having ordinary skill in the art by indicating that the sequence is present in other organisms, e.g. human, and how the level of the sequence would be used.

The Examiner states

> figure 2 and example 1 does not provide any guidance on how to determine that the expression level of SEQ ID NO. [7] is predictive of graft reaction when both the tolerance and rejected models have decreased expression levels.

However, as described above, the modified level of SEQ ID NO. 7 that is used to detect graft reactions is based on a comparison against control levels. The FIG. 2 data, presented in logarithmic scale, clearly indicates a difference between the level of SEQ ID NO. 7 in rejection-developing and tolerance-developing receptor animals. The difference in expression levels between control and tolerance-developing receptor animals, as recited in the claimed method, is used to determine rejection reaction over time, and not the absolute level of expression. Thus, Applicants respectfully assert that the specification does enable a person having ordinary skill in the art to predict graft reaction based on a determination of the expression of SEQ ID NO. 7.

The Examiner states

> it can not be concluded that an increased level of SEQ ID NO. 7 is indicative of accepted graft as neither figure 3 nor figure 4 demonstrate that the expression level of SEQ ID NO. 7 increases.

FIGS. 3 and 4 and p. 19 designate that animals treated with the antibodies DST+YTS177 were designated as "tolerance developing receptor animals". In fact, these animals do not develop tolerance and show a chronic rejection. Thus, FIGS. 3 and 4 show two types of rejection, acute (squares "Co") and chronic (circles "DST+177"), but no tolerance. Chronic rejection requires an intensified monitoring of the patient and increased immunosuppression compared to patients showing acceptance. Thus, a decrease of SEQ ID NO. 7 enables detection of both types of rejection, chronic and acute.

Acute and chronic rejections must be distinguished because patients that develop an acute rejection need intensified treatment. Episodes of acute rejection contribute to impaired long term graft outcome. Thus, early prediction of acute rejections allows early therapeutic intervention. Conversely, for a patient developing tolerance, little if any therapeutic intervention (e.g., immunosuppressive drugs) is required, preventing development of side effects such as nephrotoxicity, severe infections, or tumor formation. For a patient developing a chronic rejection, continued treatment and monitoring are required. Currently, once a developing chronic rejection is recognized by a slow fall in graft function, no therapeutic intervention is possible. An earlier diagnosis of chronic rejection would enable therapeutic intervention and thereby improve long term graft outcome.

The Examiner also presents arguments regarding use of statistical methods and that the specification only evaluates data based on "only one rejected graft animal and one accepted graft animal for kidney and heart grafts and only one accepted graft animal for liver grafts". Applicants assert that each of FIGS. 2-4 show error bars of a statistical analysis, demonstrating that a number of animals were analyzed. In addition, Applicants assert that statistically relevant results have been described in the specification for a number of animal models and a number of different transplants. Data were analyzed using the statistical software SPSS (SPSS GmbHSoftware, Munich Germany) and are reported as mean ± SD. Data for gene expression between treatment groups, (e.g. between a control group and a treatment group) were analyzed by the Friedmann test, followed by using the MWU test for pair-wise comparison. Differences were considered significant when $p < 0.05$. Applicants also submit a copy of these findings as published (American Journal of Transplantation, 7 (2007) 1091, attached Exhibit B), indicating these results have been accepted by the scientific community.

Thus, for at least the reasons described above, Applicants respectfully assert that the specification enables a person having ordinary skill in the art to practice the claimed method and respectfully requests withdrawal of the rejection of claims 40-46 and 48.

CONCLUSION

Applicants believe the application is in condition for allowance. Payment of the three month extension fee is being simultaneously made by Electronic Funds Transfer. No other fees are believed due but, if deemed necessary, the Office is authorized to charge fees to Deposit Account No. 20-0809.

The Examiner is invited to contact Applicants' undersigned representative with questions.

Respectfully submitted,
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